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MANAGEMENT OF ENDOCRINE DISEASE

Fertility, pregnancy and lactation in women with adrenal insufficiency

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Abstract

With the introduction of hormonal substitution therapy in the 1950s, adrenal insufficiency (AI) has been turned into a manageable disease in pregnant women. In fact, in the light of glucocorticoid replacement therapy and improved obstetric care, it is realistic to expect good maternal and fetal outcomes in patients with AI. However, there are still a number of challenges such as establishing the diagnosis of AI in pregnant women and optimizing the treatment of AI and related comorbidities prior to as well as during pregnancy. Clinical and biochemical diagnoses of a new-onset AI may be challenging because of overlapping symptoms of normal pregnancy as well as pregnancy-induced changes in cortisol values. Physiological changes occurring during pregnancy should be taken into account while adjusting the substitution therapy. The high proportion of reported adrenal crisis in pregnant women with AI highlights persistent problems in this particular clinical situation. Due to the rarity of the disease, there is no prospective data-guiding management of pregnancy in patients with known AI. The aim of this review is to summarize the maternal and fetal outcomes based on recently published case reports in patients with AI and to suggest a practical approach to diagnose and manage AI in pregnancy.

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Background and epidemiology

Adrenal insufficiency (AI) can either be caused by destruction of the adrenal glands through different mechanisms with glucocorticoid, mineralocorticoid and/or androgen deficiencies (primary AI), or may occur as a result of dysfunction of the pituitary with adrenocorticotrophic hormone (ACTH) deficiency (secondary AI) or of the hypothalamus with corticotropin-releasing hormone (CRH) deficiency (tertiary AI). In developed countries, autoimmune adrenalitis is the

most common cause of primary AI, which may occur in isolation or as part of an autoimmune polyglandular syndrome (APS). APS type 2 is the most common form presented as a combination of Addison's disease, thyroid autoimmune disease, type 1 diabetes and/or premature ovarian failure. Type 1 and type 4 APS may also present with primary AI. In developing countries, tuberculosis with the involvement of the adrenal glands is still more common than autoimmune adrenalitis as a cause

Invited Author's profile

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of primary AI. Other causes include fungal infections, adrenal hemorrhage, metastases or infarction involving both adrenal glands. Congenital adrenal hyperplasia as another cause of primary AI will not be discussed in this review.

Prolonged exogenous glucocorticoid administration for various conditions (such as asthma, rheumatoid arthritis and inflammatory bowel disease, among others) is the most common cause of combined secondary and tertiary AIs due to impaired ACTH and CRH secretion. Other pregnancy-related causes of secondary AI are Sheehan's syndrome (due to postpartum pituitary necrosis) and lymphocytic hypophysitis occurring preferentially in postpartum setting or in the last trimester. A structural disease of the pituitary as a cause of secondary AI is mostly known and treated before conception. Similarly, all patients with bilateral adrenalectomy due to Cushing syndrome (CS), or with unilateral adrenalectomy due to a benign or malignant adrenal tumor, and after cranial radiotherapy, most likely have an established endocrine follow-up and optimal glucocorticoid replacement therapy where needed.

Although AI is very rare in pregnancy, yet it can lead to significant maternal and fetal morbidities if the diagnosis is missed during pregnancy or in the puerperium. In fact, prior to the introduction of glucocorticoid replacement therapy, Addison's disease was associated with a high maternal mortality (35–45%), so that women were strongly discouraged from becoming pregnant (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11). Modern glucocorticoid replacement therapy and improved obstetric care have both contributed immensely in reducing maternal as well as fetal morbidity and mortality. Nowadays, an uneventful pregnancy with good maternal and fetal outcomes can be expected in the majority of patients with known AI (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12).

The exact prevalence of AI in pregnancy is unknown. Schneiderman and coworkers reported the incidence of primary AI to be 1 in 3000 pregnancies in a population-based cohort study on 7.7 million births with an observed increase in prevalence of Addison's disease from 5.6 per 100 000 in 2003 to 9.6 per 100 000 in 2011 (13). In the literature (as summarized in Table 1), the underlying reasons for AI in pregnant patients are evenly distributed between primary (44%) and secondary (45%) causes, which also defines the presence of potential hormonal comorbidities. The most commonly reported coexisting endocrine disorders are hypothyroidism (50%) and a few cases of type 1 diabetes, among others.

Effects of the feto-placental unit on steroid metabolism

The feto-placental unit is actively controlling the steroid milieu of the fetus. Additionally, it is responsible for various changes in the maternal hypothalamic pituitary adrenal (HPA) axis leading to a state of physiological hypercortisolism in pregnancy (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12).

In healthy pregnant women, total and free plasma cortisol, ACTH, CRH, cortisol-binding globulin (CBG) and urinary-free cortisol increase (13, 14, 15, 16). The placenta can itself produce biologically active CRH and ACTH stimulating the maternal pituitary and adrenal glands, respectively. CBG increases 3–4-fold following estrogen stimulation, thereby not only increasing the half-life of cortisol but also increasing total plasma cortisol values. Free cortisol increases by the 11th week of gestation. In contrast to CS, circadian rhythmicity is maintained throughout pregnancy implying an altered set point of the HPA axis and a relative tissue refractoriness to the effects of cortisol in pregnancy (13, 14, 15, 17).

Similarly, the activity of the renin-angiotensin-aldosterone system is increased by the 8th week of gestation. On the other hand, progesterone exerts anti-mineralocorticoid effects and results in a decrease in systemic vascular resistance. As a combined effect of these mechanisms, there is a net volume expansion during pregnancy (14).

Up to the 33rd week of gestation, 90–95% of fetal cortisol is derived from maternal adrenal secretion; thereafter, fetal adrenal cortisol production progressively increases with decreased maternal contribution. In cases of unrecognized maternal AI, transplacental passage of cortisol from the fetus to the mother might have a partial protective effect during the last trimester. On the other hand, the fetus is relatively protected from excessive hydrocortisone by the placental 11- β hydroxysteroid dehydrogenase 2 even in women receiving supra-physiological doses of glucocorticoid treatment (5).

Fertility and preconceptional considerations

In the majority of cases (75.8%; Table 1), AI is present and known well before pregnancy. Therefore, there are specific considerations to be taken into account before planning a pregnancy such as optimizing the glucocorticoid treatment and screening for comorbidities to optimize chances of conception. Erichsen and colleagues performed a survey

Table 1 Overview in clinical annotations in pregnant patients with adrenal insufficiency. A Pub-Med search was performed on published English and German written articles from 1976 onward using keywords such as adrenal insufficiency, lactation and infertility. A detailed review of literature citations provided further references. To ensure evaluation of cases in the context of modern treatment, only cases dating 1976 onward were considered for inclusion (8, 20, 26, 27, 28, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52). This search identified 28 cases of primary AI, a case series with 17 cases of treated adrenocortical carcinoma patients, out of which 7 were included as they were on hydrocortisone treatment following surgical treatment (51), a literature review of 27 patients with secondary AI (20) and a literature review of 21 cases of acute Sheehan's syndrome (29).

Reference	Year	Country	Patients, n		Pregnan- cies, n	PM/MP	Time of diagnosis of AI*		Etiology of AI*	Adrenal crisis	Treatment*	Other diseases*	Mode of delivery*	Outcome	
			n	Age			Mother	Child							
(32)	1976–1987	Norway	5	19–45	6	n.a.	Before (3)	PAI (5)	Y (2/5)	HC/FC (3) Cortisone (2)	n.a.	V (5), CS (1)	Good (5)	Good (6)	
(33)	1984	Canada	1	31	1	MP	After	PAI	Y	HC/FC	HPT	CS	Good	IUGR	
(34)	1984	Italy	1	27	1	MP	Before	PAI	N	Cortisone	None	V	Good	Good	
(35)	1989	Germany	1	29	1	n.a.	Before	PAI	Y	HC/FC	HPT	V	Good	Good	
(28)	1989	South Africa	1	35	2	P2	third TM (P1)	PAI	Y	HC/FC	None	V	Good (2)	P1: Stillbirth; P2: Good	
(36)	1992	USA	1	40	1	P2	Third TM	PAI	Y	Pred/FC	HPT	CS	Good	IUGR	
(37)	1993	Germany	1	30	1	P2	After	PAI	Y	Glucocorti- coids	None	CS	Good	Good	
(8)	1997	UK	1	44	1	MP	First TM	PAI	Y	HC/FC	HPT	V	Good	Good	
(38)	1999	Israel	1	25	1	P1	After	SAI	N	HC	n.a.	CS	Good	Good	
(26)	2001	UK	1	33	1	P1	First TM	PAI	Y	HC	None	n.a.	Good	Death (Abortion)	
(39)	2003	Turkey	1	22	1	P1	first TM	PAI	Y	Pred	None	CS	Good	Good	
(40)	2003	Czech Republic	1	29	1	P1	Before	PAI	Y	HC/FC	T1D/HPT	CS	Good	Good	
(41)	2003	Ireland	1	28	1	P1	Before	PAI	N	HC/FC	None	CS	Good	Good	
(42)	2005	Greece	1	32	1	P1	Before	PAI	Y	HC/FC	HPT	V	Good	Good	
(43)	2005	Italy	1	34	1	P1	Before	PAI	Y	HC/FC	HPT	CS	Good	Good	
(27)	2008	Argentina	3	22–36	3	n.a.	Before (2); first TM (1)	PAI (3)	Y (2/3)	HC/FC (3)	None (3)	n.a.	Good (3)	Good (2)	
(44)	2009	Italy	1	36	1	P1	Before	PAI	N	Cortisone/FC	None	CS	Good	Good	
(20)	2009	Finland	27	27–42	31	n.a.	Before (n = 27)	SAI (27)	n.a.	n.a.	n.a.	n.a.	Good	Good	
(45)	2010	Poland	1	21	1	P1	First TM	PAI	Y	HC/FC	None	V	Good	Good	
(46)	2010	Poland	1	32	1	P2	Second TM	PAI	Y	HC/FC	HPT	CS	Good	IUGR	
(47)	2011	India	1	33	1	P3	Second TM	PAI	Y	HC/FC	None	CS	Good	Good	
(48)	2011	Poland	1	31	1	P2	Second TM	PAI	Y	HC/FC	HPT, DI	V	Good	Good	
(49)	2012	India	1	29	1	MP	Third TM	PAI	Y	Pred/FC	HPT	V	Good	Good	
(50)	2014	Spain	1	34	1	P1	Before	PAI	N	HC	T1D	CS	Good	Good	
(51)	2015	ENSAT	7	n.a.	7	n.a.	Before (7)	PO- ACC (7); Sheehan/SAI	n.a.	HC	n.a.	n.a.	Good (7)	Good	
(29)	2017	Japan	1	27	1	P2	After P1	PAI: 28/64	n.a.	HC	Pan-HPT	V	Good	Good	
Total			64	P1: 10/21 (47.6%); P2: 6/21 (28.6%); P3: 1/21 (5%); MP: 4/21 (19%)	70		Before: 47/62 (75.8%); first: 5/62 (0.08%); second: 3/62 (0.05%); third: 3/62 (0.05%); after: 4/62 (0.06%)	PAI: 28/64 (44%); SAI: 29/64 (45%); PO- ACC: 7/64 (11%)	Y: 20/29 (69%); N: 9/29 (31%)	HC: 11/37 (29.7%); HC/FC: 18/37 (48.6%); other: 8/37 (21.6%)	None: 12/24 (50%); HPT: 10/24 (41.7%); others: 4/24 (16.7%)	V: 14/27 (51.9%); CS: 13/27 (48.1%)	Good: 64/70 (91.4%); IUGR: 3/70 (0.04%); stillbirth: 1/70 (0.01%); abortion: 1/70 (0.01%); neonatal death: 1/70 (0.01%)		

*numbers within parentheses in these columns indicate *n*; ACC, adrenocortical carcinoma; CS, caesarian section; FC, fludrocortisone; good, alive; HC, hydrocortisone; IUGR, intrauterine growth retardation; PP, primipara; MP, multipara; n.a., not available/not applicable; Y, yes; N, no; PO-ACC, postoperative ACC; PAI, primary AI; P1, primipara; SAI, secondary AI; HPT, hypothyroidism; T1D, type 1 diabetes; TM, Trimester; Y, yes.

Review	G Anand and F Beuschlein	Pregnancy and adrenal insufficiency	178:2	R48
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in 269 females of the Norwegian Addison's registry with 174 women (65%) participating in the survey. The author found a decreased standardized incidence ratio of 0.69 for birth (confidence interval, 0.52–0.86) as a proof of reduced fertility in females with Addison's disease after excluding women with premature ovarian insufficiency (18). In untreated patients with primary AI, fertility can be reduced due to decreased generalized sense of well-being and reduced libido due to the lack of androgens among other mechanisms. Despite androgen depletion, impaired sexuality had not been reported in the mentioned study (18) and a common reason for sexual inactivity – the lack of a partner – has also to be considered.

Coexisting autoimmune disorders such as thyroid disease and premature ovarian insufficiency are other reasons for reduced fertility in patients with primary AI. Similarly, a common cause of reduced fertility in patients with pituitary disease is altered gonadotropin secretion. Overall, concomitant hormonal deficiencies should be addressed to enable conception in a patient with known AI as fertility may in fact be mainly reduced due to these hormonal deficits. For example, patients with complete loss of pituitary function need assistance of artificial reproductive techniques to conceive. These pregnancies are considered as high-risk (19, 20).

In addition to issues of fertility, a main focus of preconception endocrine counseling should be patient education regarding the need of treatment adjustment during gestation, especially during stress states. Also, the obstetrician should be informed regarding the need of adjustment of glucocorticoid dose in stress situations such as infections, hyperemesis and delivery. In fact, as discussed below, delivery can be considered as one of the most stressful situations, where use of an established protocol of parenteral stress dose glucocorticoid application could help in assuring optimal management.

Establishing the diagnosis of a new-onset AI during pregnancy

In general, the slowly progressive course of AI makes early diagnosis challenging. It is believed that more than 90% of the cells of adrenal cortex are destroyed before clinical manifestations of primary AI become apparent (21). Pregnancy can mirror some of the symptoms of AI and a biochemical diagnosis of a mild AI may be particularly challenging due to physiological state of hypercortisolism. Therefore, it is prudent to include AI in the differential diagnosis in patients presenting

with excessive fatigue, malaise, weight loss, vomiting, dizziness, hyperpigmentation, abdominal pain and/or electrolyte disturbances. Clinical suspicion should be particularly high in patients with personal or family history of an autoimmune disease (16). In contrast to chloasma of pregnancy, hyperpigmentation of Addison's disease involves non-exposed parts of skin/creases of hands, extensor surfaces and mucous membranes. Salt craving, hyponatremia with more than 5 mmol/L decrease in plasma sodium and metabolic acidosis are other specific clues for AI. As expected and according to the reviewed literature (Table 1), onset of AI within pregnancy accounts for only a minority of patients (17.7%) with even distribution over the duration of the pregnancy (first trimester; 8.1%, second trimester; 4.8% and third trimester; 4.8%, respectively).

Acute presentation can occur with adrenal crisis in stressful situations encountered in early pregnancy (hyperemesis gravidarum), infections during pregnancy/ puerperium, operations or delivery (both vaginal and cesarean). In the case of severe AI, it is of utmost importance to initiate treatment with hydrocortisone before awaiting results of laboratory tests and testing can even be postponed until stabilization of the patient's condition. In the event of obstetric hemorrhage where tachycardia and hypotension persist after adequate replacement of blood products, the possibility of acute Sheehan's syndrome should be kept in mind and minimal investigation including baseline levels of ACTH, cortisol, prolactin and free thyroxine should be undertaken.

Currently, paired measurement of early morning cortisol and ACTH is recommended as screening investigation to diagnose primary AI. A low early morning cortisol <5 µg/dL in the setting of typical clinical symptoms is sufficient to confirm the diagnosis of AI and when accompanied with raised ACTH levels (>2-fold the upper limit of reference range) also establishes its cause to be primary AI. In equivocal cases with early morning cortisol between 5 and 32 µg/dL depending on the trimester, it is safe to employ the corticotropin stimulation test as diagnostic 'gold standard' (5). Suri and coworkers demonstrated higher peak cortisol responses of up to 36 µg/dL to 250 µg/dL of cosyntropin in 36 healthy pregnant women in the second and third trimesters. As a result, many authors suggest the use of trimester-specific cut-offs for stimulated cortisol values in the first, second and third trimesters of 25, 29 and 32 µg/dL, respectively, to diagnose or exclude AI (3, 6, 12, 17). Additionally, validated antibody assays should be used as adjuvant tests as 21-hydroxylase antibodies are positive in >90% of the

patients and 17-hydroxylase antibodies in 30% of the patients with primary AI (22).

In cases with recent onset of secondary AI, corticotropin stimulation tests may give misleading results as adrenals may still respond normally to exogenous ACTH. However, insulin hypoglycemia testing is contraindicated in pregnancy due to safety reasons. Suri proposed the use of salivary cortisol as a more physiological measure of adrenal reserve in pregnancy (23) but it remains a challenge to diagnose or exclude AI based on these measures only. Fortunately, a new-onset secondary AI due to a structural disease of pituitary is very rare in pregnancy. These patients may also have additional symptoms such as headache or visual disturbances due to mass effects of a pituitary tumor. However, lymphocytic hypophysitis might present preferentially in the last trimester or postpartum. While treatment of secondary AI and secondary hypothyroidism is of particular importance during pregnancy, imaging can be delayed until delivery in patients without symptoms of mass effect. In the case of need to evaluate visual symptoms, MRI without contrast should be used in pregnant patients.

Substitution and dosage adjustment during pregnancy

The main aim of substitution therapy is to avoid both under- and over-replacement of glucocorticoid and mineralocorticoid treatments and to prevent adrenal crisis. Undesirable effects of over-replacement are increased risk of gestational diabetes, hypertension/preeclampsia, weight gain and bruising. In contrast, low substitution dosages might increase the risk of hyperemesis and put the patients at risk to develop an acute adrenal crisis.

Hydrocortisone has been advocated as the glucocorticoid substitution of choice. Accordingly, in the majority of reported cases in the literature, hydrocortisone is used (in 78.4% either alone or in combination with fludrocortisone; Table 1). High-dose glucocorticoid treatment is considered teratogenic in rodents causing cleft palate, fetal death and placental degeneration (24). In contrast, hydrocortisone exposure in humans is considered safe probably because of different glucocorticoid receptor–ligand systems and because of placental 11- β -hydroxysteroid dehydrogenase type 2 inactivating cortisol.

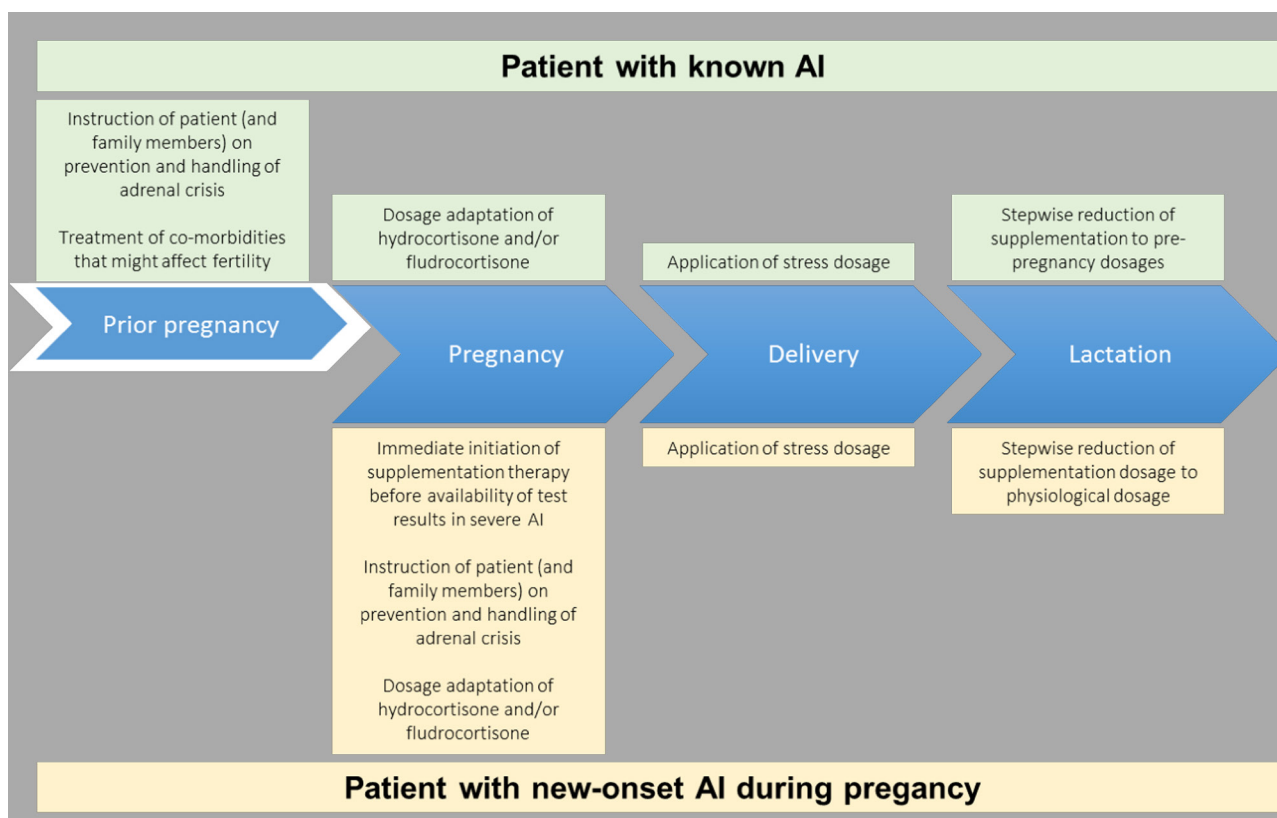


Figure 1

Overview on diagnostic and therapeutic considerations in patients with newly diagnosed or known adrenal insufficiency (AI).

Review	G Anand and F Beuschlein	Pregnancy and adrenal insufficiency	178:2	R50
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Based on the physiological increase in total and free cortisol values in normal pregnancy, the current approach is to increase hydrocortisone doses up to 20–40% in the last trimester (3). Due to the lack of sufficient evidence, patients should have clinical follow-up once every trimester with dosage adaptation based on the individual course of pregnancy as illustrated in the flow diagram (Fig. 1). Labor is a state of increased glucocorticoid requirement and should be preferably managed with hydrocortisone stress dose (100 mg hydrocortisone intravenously) followed by a continuous infusion of 100–200 mg/24 h at the beginning of the second stage of labor (3, 4, 5, 6). Similarly, hydrocortisone stress dose can be given as premedication followed by a continuous infusion of 100–200 mg/24 h in case of cesarean section. We suggest stepwise reduction of hydrocortisone supplementation therapy after the stress phase of delivery has passed. The duration of this transition period is mostly 24–48 h after delivery but may vary in individual cases.

Fludrocortisone is mostly used as a mineralocorticoid replacement in Addison's disease. In fact, mineralocorticoid requirement may slightly increase in the last trimester due to anti-mineralocorticoid effects of progesterone. Clinical parameters such as signs of orthostatic hypotension and increase in serum potassium should govern dose adjustment. Likewise, fludrocortisone must be reduced in cases of hypertension and or hypokalemia and even be withdrawn in cases of preeclampsia. In contrast, plasma renin cannot be used as a reliable marker to adjust mineralocorticoid dosing in pregnancy.

Management of adrenal crisis

As there had been no clear definition of adrenal crisis, in 2015 Alolio proposed a definition of adrenal crisis as a profound impairment of general health and the presence of at least two of the following signs or symptoms: hypotension (systolic blood pressure <100 mmHg), nausea or vomiting, severe fatigue, hyponatremia, hypoglycemia and hyperkalemia, making subsequent parenteral glucocorticoid administration necessary (25). According to the current literature search, a high incidence of adrenal crisis in pregnant women with AI of 69% can be assumed (Table 1) despite the fact that this clear definition had not been met in all cases. Although this percentage could also be an overestimation due to general over-reporting and due to the initial clinical presentation of newly diagnosed patients, adrenal crisis remains a clinically

relevant problem. The probable triggers of adrenal crisis during pregnancy are hyperemesis, infections and non-adherence to substitution therapy.

Patient and partner education to adjust the hydrocortisone dosage in stressful situations and instruction to self-inject hydrocortisone are important measures to prevent an impending adrenal crisis. The main aims for the treatment of adrenal crisis are to treat hypotension with rapid fluid replacement and to reverse glucocorticoid deficiency with parenteral hydrocortisone (12). These aims also apply to pregnant women with additional attention to fetal monitoring to assure the well-being of the unborn child.

Outcome of pregnancies in AI

In the recent literature, there is no report of maternal death with a direct relation to the presence of AI (Table 1). In contrast, unfavorable outcomes of pregnancies have been described with intrauterine growth retardation (IUGR) being the most common (4.2%; Table 1). In an analysis of 31 pregnancies in 27 women with hypopituitarism of different etiologies, the rate of children who were small for gestational age was found to be higher (38% vs 12.7% in IVF control pregnancies) (20). As a potential cause, poor placental function was proposed in these women. In addition to growth retardation, there were more cesarean deliveries (89% vs 11.4%), more transverse lies (15% vs 2.1%) and more postpartum hemorrhages (5.26% vs 1%) (20). High rate of cesarean section was partly due to more malpresentations and partly due to obstetrician's recommendation.

Gradden and colleagues reported on an abortion in the 11th week of pregnancy in a previously unknown case of primary AI, where the diagnosis was delayed as symptoms were initially thought to be related to hyperemesis of pregnancy (26). Furthermore, Otta and coworkers described one case of neonatal death from a mother with known primary AI occurring 20 h after birth due to acute cardiorespiratory failure (27). In this case, the patient was reported to be non-adherent to the recommended glucocorticoid treatment throughout the gestation period. In addition, Seaward and colleagues reported on two pregnancies in a patient, where stillbirth occurred in the first pregnancy at 31st week of gestation due to placental disruption (28). In this case, the patient also suffered from adrenal crisis before delivery, while the course of a second pregnancy was uneventful.

Lactation in the context of AI

Lactation can itself be affected by comorbidities of AI including pituitary insufficiency. Matsuzaki and colleagues compiled 21 cases of acute Sheehan's syndrome from the literature (1990–2014) and included his own rare case of a successful second pregnancy after induction of ovulation in a patient with Sheehan's syndrome under replacement treatment with hydrocortisone and thyroxine (Table 1 describes only his case). The authors reported variable onset of symptoms of different pituitary hormonal deficiencies with a median time of presentation of secondary AI being 7.9 days following delivery (29).

Given the ability as well as willingness of breastfeeding in patients with AI, the question arises, whether glucocorticoid substitution could potentially affect the child. In 1975, McKenzie and colleagues reported negligible excretion of prednisolone in breast milk over a period of 48 h after receiving 5 mg of 3^H -prednisolone (range: 0.07–0.23% of the dose/L of milk/day). The authors concluded that the exposure of the suckling infant through the breast milk would be extremely small in a woman receiving 30 mg of prednisolone daily (30). Similarly, Öst and coworkers examined prednisolone excretion in milk in 6 lactating women receiving daily prednisolone doses ranging from 10 to 80 mg and concluded that even at a daily dose of 80 mg prednisolone, the infant would ingest <0.1% of that dose (31). These early studies indicate that the physiological dose of glucocorticoid required to substitute AI is unlikely to cause harm in breast-fed children.

Key points

In summary, there are a number of pathophysiological consequences of AI that can directly or indirectly affect pregnancy and complicate medical care of these patients. Overall, one can expect good maternal and fetal outcomes in properly treated patients with AI, which should reassure affected patients. However, the high proportion of reported adrenal crisis provides clear evidence that these patients require good education of their disease and close monitoring in specialized centers.

A new diagnosis of AI during pregnancy poses challenges due to the rarity of the disease, overlapping symptoms with normal pregnancy and difficulties in establishing biochemical diagnosis in mild cases. Consultation of an endocrinologist in a patient presenting with suggestive symptoms of AI should help in early diagnosis and management.

Clearly, many questions remain unanswered because of the lack of prospective data. Given the rarity of AI, we suggest collection of prospective information in pregnant patients as part of international registries.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

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